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Radiation Therapy for Synchronous Basal Cell Carcinoma and Lentigo Maligna of the Nose: Response Assessment by Clinical Examination and Reflectance Confocal Microscopy

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Introduction

Radiation therapy (RT) is a non-invasive treatment for a variety of skin cancers. While surgery is often preferred for basal cell carcinoma (BCC) and lentigo maligna (LM), these conditions often affect patients that are medically inoperable, who decline surgery, or have lesions in challenging anatomic locations. While non-surgical treatments can be employed, close monitoring for disease recurrence and progression is of utmost importance. Typically this is carried out by clinical examination, without adjunctive imaging. Reflectance confocal microscopy (RCM) is an emerging imaging technology that is proving useful to aid in the assessment of treatment response and disease recurrence (Figure 1). RCM has a high sensitivity (93%) and specificity (82%) for diagnosing lentigo maligna (Odds Ratio = 60.8), and is FDA approved for “review by physicians to assist in forming a clinical judgment” [1]. Herein, we describe the case of a patient with a synchronously occurring BCC and LM of the nose, treated with definitive RT, and evaluated pre- and post-RT with RCM, which demonstrated complete response of the BCC and eventual recurrence of the LM.

Case Report

An 83-year-old woman with a history significant for several non-melanoma skin cancers and stage IV mantle cell lymphoma presented for management of a microinvasive lentigo maligna of the nasal tip (Figure 2A). At initial consultation, mapping RCM using the handheld Vivascope 3000 (Caliber I.D. (formerly Lucid Inc.), Rochester, NY) was

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performed and revealed areas of dendritic melanocytes and pagetoid cells diagnostic of melanoma, as well as areas of polarized nuclei, tumor nests, and elongated blood vessels diagnostic of BCC (Figures 2B and 2C). Biopsies of these confocally suspicious areas to define the extent of the lesion revealed a multifocal BCC superior and lateral to the LM (Figures 2D and 2E). In light of the multifocal nature of the BCC and melanoma on the nasal bridge, the patient declined surgery due to risk of significant disfigurement.

To treat both skin cancers the patient elected to undergo definitive, curative-intent RT directed at the entire nose. She was treated with a prescription dose of 57.5 Gy in 23 fractions at the 96% isodose line (Figure 3C) using parallel opposed lateral 6 MV photon fields (Figure 3B) produced by a linear accelerator. A custom wax block bolus was created to allow for adequate dose buildup. Skin surface dose was measured in triplicate by optically stimulated luminescent diodes which confirmed the skin surface received 101.4% of the prescription dose. Treatment was carried out as planned with no interruptions or delays. The patient experienced the expected acute effects of radiotherapy including grade 2 dermatitis (Figure 3A) and mucositis, as well as grade 1 pruritus and fatigue. At four months post-radiation therapy, there was a complete clinical response with resolution of all apparent hyperpigmentation (Figure 4A); however, there were persistent features of LM by RCM including atypical cells and architectural pleomorphism, and subtle signs of BCC on RCM including tumor nests and clefting (Figure 4B and 4C). One year following treatment, a pigmented macule appeared on the nasal tip which enhanced on Wood's lamp examination (Figure 5A). RCM at that time revealed multiple large pagetoid dendritic cells in the epidermis, suggesting recurrence of the LM. No signs of BCC were noted by RCM (Figures 5B and 5C). The patient declined biopsy or topical treatments at that time and she elected to observe the lesion clinically, given concerns over side effects from treatment. The patient has remained asymptomatic with stable hyperpigmentation on exam, and RCM has been performed every 3 months (latest visit 21 months post-RT) with no evidence of dermal invasion detected.

Discussion

Radiation therapy serves as a viable alternative for treatment of BCC and LM when the patient has comorbidities that limit surgery or when these lesions occur in areas where excision may result in significant cosmetic and/or functional deficit. One advantage of RT over surgery is the preservation of normal tissue within the radiation field. Treating the patient with a highly fractionated course allows for selective killing of tumor cells and sparing of normal tissues, as normal cells are able to repair some degree of radiation damage while malignant cells cannot, leading to their death.

A recent systematic review by Fogarty *et al.* in 2014 developed a series of recommendations for defining the field and dose as well as monitoring outcomes, including progression to invasive melanoma, monitoring for recurrence, and optimizing cosmetic or functional outcomes [2]. Traditionally, the radiation field was determined by the visible lesion plus a margin extending equally in all directions. They recommended using a dose of at least 54 Gy in 27 fractions of 2 Gy as definitive treatment, but no more than 60 Gy in 30 fractions of 2 Gy [2]. In our case, the dose of radiation used was based on a small Australian report that

demonstrated a 100% rate of control [3], and falls within the recommended guidelines proposed by Fogarty *et al.* [1]. According to NCCN guidelines, 57.5 Gy in 23 fractions is also an adequate dose of radiation therapy for basal cell carcinoma [4].

Recently, RCM has been implemented as a tool to evaluate these clinically complex skin cancers. RCM provides non-invasive evaluation of the skin with cellular-level resolution and can be used for mapping discrete borders of subtle LMs. There is a learning curve associated with RCM imaging; however, the training required for accurate RCM interpretation has been reported to be less than that of dermoscopy [5]. Practical limitations to widespread adoption of RCM include its high cost relative to dermoscopy (approximately \$50,000 for the handheld Vivascope 3000) [6], a limited depth of imaging (250-300µm), and time required for imaging large lesions. Although more onerous than dermoscopy, RCM provides detailed images of live tissue and can reconstruct 3D areas for evaluation, critical for assessing LMs with poorly defined borders that may have significant subclinical extension. As such, RCM is a valuable adjunct to the clinical exam and dermoscopy to determine clinical margins and define the gross tumor volume for radiation planning.

LMs treated with radiation have a 5% recurrence rate with a median follow-up time of 3 years [2]. Recurrence can be difficult to detect clinically, as it may manifest as an amelanotic lesion, or may be obscured by radiation-induced inflammation and post-radiation pigment changes. Because RCM allows for the same area of skin to be re-examined over time, this technology is used to monitor for recurrence in LMs [7]. After RT, LM-specific large pagetoid cells were decreased or even resolved in the epidermis, dermal-epidermal junction, and in the follicles [8]. Observed changes in LMs after radiation include superficial necrosis and apoptotic cells, dilated vessels, and increased inflammatory cells in both the dermis and epidermis [8]. When using RCM to monitor for recurrence post-treatment, it is important to wait long enough to ensure any acute radiation-induced changes in skin architecture have resolved and will not cause false positives [9]. The ability to visualize and define changes during and after RT suggest RCM may be useful for monitoring for treatment failure.

In our patient, examination with RCM one year after completing RT highlighted concerning features for local LM recurrence, including multiple large pagetoid dendritic cells, epidermal disarray, and perifollicular infiltration. While biopsy was declined by the patient to confirm this, possible explanation for recurrence in our patient are the microinvasive component and adnexal involvement that herald more significant disease burden and lower likelihood of treatment success.

Conclusion

Non-surgical therapies are often appropriate alternatives for the treatment of complex superficial skin cancers, especially in the elderly. This case highlights both the promise and challenges associated with radiation therapy in this setting. It further underscores the potential role of RCM to facilitate mapping lesions pre-treatment as well as its longitudinal function in assessing response and monitoring for progression or recurrence in patients

treated with radiation. Further studies on the use of RCM to monitor skin cancers treated with non-surgical methods are warranted.

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Figure 1. Vivascope Reflectance Confocal Microscope System. Inset shows the handheld Vivascope 3000 as it is used to evaluate a skin lesion.

Figure 2.

A) Lentigo maligna of the right nasal tip presenting as a hyperpigmented patch with poorly defined borders (yellow arrow). Mapping biopsies guided by reflectance confocal microscopy showed clinically occult basal cell carcinoma at the sites indicated by the blue arrows.

B) RCM evaluation of the hyperpigmented patch identified sheets of atypical dendritic cells (yellow arrowheads) and epidermal disarray around adnexal structures.

C) RCM identified areas of tumor nests (blue circle) and dilated blood vessels suspicious for BCC.

D) Shave biopsy of the right nasal tip showing melanoma in situ extending to the margins (Hematoxylin and Eosin, 200x).

E) Mapping biopsies surrounding the hyperpigmented patch identified BCC encroaching on the melanoma (Hematoxylin and Eosin, 40x).

Figure 3.

A) Clinical photograph at the end of radiation therapy showing erythema and inflammation in the irradiated area.

B) Digitally-reconstructed radiograph with beam aperture from the right lateral field.

C) Isodose distributions from treatment plans in the axial plane at the level of the nose. Colored lines represent the different isodose lines.

Figure 4.

A) Clinical photograph taken four months post-radiation therapy show resolution of the clinically apparent lentigo maligna. RCM demonstrated persistent signs concerning for lentigo maligna at the yellow arrow (Figure 3b) and subtle findings suggestive of BCC at the blue arrow (Figure 3c).

B) Large, atypical dendritic pagetoid cells (yellow arrowheads) identified by RCM suggestive of persistent lentigo maligna at the nasal tip.

C) Subtle areas of tumor nests with clefting (blue circles) identified by RCM at the site previously confirmed as BCC.

Figure 5.

A) Clinical photograph at one year following radiation therapy recurrence of hyperpigmentation suggesting recurrence of lentigo maligna (yellow arrow). Area identified by the blue arrow was examined with RCM and did not find features of BCC.

B) RCM identified large, hyperreflective pagetoid cells (yellow arrowhead) and perifollicular infiltration (yellow circle) consistent with lentigo maligna.

C) RCM failed to identify features suggestive of persistent BCC at the previously positive site.